REMARKS

Claims Rejection Under 35 U.S.C. §112

Claims 1, 3, 5-14 and 16-57 have been rejected under 35 U.S.C. §112 ¶ 1 for allegedly not complying with the written description requirement. Of the claims rejected under §112 ¶ 1, claims 1, 5, 6, 10, 14 and 16-57 are still pending. Applicants have amended claims 1, 5, 10, 14, 19, 40, 47 and 57.

Claim 1 has been amended to recite that the nucleic acid molecule consists essentially of nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49, or SEQ. ID NO:50. Each of claims 5, 6, 10 and 14 further define that which is recited in claim 1. Because these claims recite specific nucleotide sequences, for which specific structure and function were included in the specification (or drawings) when the application was filed, the written description requirement is clearly met.

Claims 16-56 are directed to nucleic acid vectors, bacteria transformed with those vectors and methods of overexpressing a gene using the transformed bacteria. As will be explained in detail below, each of these claims recites adequate structure and function of the claimed vectors, which is well supported and adequately defined in the original specification.

It is well settled that a patent specification satisfies the written description requirement of §112 ¶ 1 if it describes the claimed invention in sufficient detail that one skilled in the art would understand that the inventor had possession of the claimed invention at the time the application was filed. Possession of the claimed invention can be shown using words, structures, figures, diagrams and formulas that set forth all of the elements of the claimed invention. Possession can be demonstrated with a description of an actual reduction to practice, or by establishing that the invention was ready for patenting by showing that the invention was complete at the time the

application was filed. *See,* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement, 66 (4) Fed. Reg. 1099, 1104, January 5, 2001 (hereinafter the "Guidelines").

One way of showing that the invention was complete is by disclosing sufficiently detailed, relevant identifying characteristics that provide evidence that the applicant was in possession of the claimed invention. Sufficient evidence that the invention was complete is found if the specification includes complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of such characteristics. Guidelines at 1106. Thus, where adequate structure and its correlated function are described in the application, the written description requirement is met.

Claim 16 is directed to subject matter having such adequately described structure and its correlated function. Specifically, the claim recites a nucleic acid vector that enhances translation of a gene under conditions that elicit a cold-shock response in a bacterium. The vector includes a downstream box and a nucleic acid fragment. According to the claim, the fragment is derived from a nucleic acid molecule that includes a cold shock inducible gene, which is not included in the vector. Also according to the claim, the function of the fragment is to enhance translation of the gene under cold shock conditions.

Such vectors are described, for example, in the specification at page 28, line 8 through-page 29, line 14. Beginning at page 28, line 8 and in the examples that follow, expression plasmids and their use to transform bacteria are described. Expression plasmids and their role as vectors, in general, are well known to those skilled in the art. The particular vectors of the invention that are described in the specification include a downstream box and a nucleic acid

fragment, as recited in the claim. Further, the description of each of these elements is consistent with that recited in the claim, and includes adequate structure and function to demonstrate that Applicants had possession of the claimed invention.

The specification describes a downstream box by way of background at page 4, line 13 through page 5 line 11. The structure and function of the downstream box of the invention are described in more detail at, for example, page 17, line 18 through page 20, line 12. Specifically, the structure of the downstream box is a nucleotide sequence that is at least partially complementary to a region called the anti-downstream box ("ADB") of 16S rRNA, which in the case of *E. coli*, are bases 1469-1483 of the 16S rRNA. (page 4, lines 14-18.) The downstream box of the invention is a sequence that is typically 3' of the initiation codon and has relatively high complimentarity with the ADB of a bacterial rRNA. In addition, specific examples of downstream box sequences according to the invention are set forth on page 20 as SEQ ID Nos:2-6. The structure of the downstream box is correlated to its function, which is believed to be enhancement of translation by formation of a duplex with the ADB. (page 4, lines 18-20.) Thus, both the structure and correlated function of the downstream box are adequately described in specification.

With reference to the nucleic acid fragment, claim 16 recites that the nucleic acid fragment is derived from a nucleic acid molecule that includes a cold shock inducible gene, which gene is not included in the vector. The nucleic acid fragment enhances translation of the gene under cold shock conditions. Like the downstream box, specific sequences and their use as nucleic acid fragments in the claimed vectors are described in detail in the specification. For example, beginning at page 27 line 21, the specification describes a region situated between +117 and +143 of the 5' untranslated region ("UTR") that enhances the translatability of *cspA*

transcripts. A particular sequence, located from +123 to +135 for *cspA* mRNA is almost completely conserved among *cspA, cspB* and *cspG*, the specific sequences for each of the transcripts being shown in Fig. 12 and set forth in SEQ ID NO:48, SEQ ID NO:49, and SEQ ID NO:50, respectively. Figure 12 also shows the positions of the sequences within the transcripts. As pointed out in the specification, this translation-enhancing region is believed to be complementary to a different region of the 16S rRNA (+1023 to +1035 as shown in Fig. 12) than is the downstream box. Based on the detailed description of the translation-enhancing sequences, their high level of conservation among the transcripts, the proximity of location of the sequences within each transcript, and their complementation with a specific region of 16S rRNA, one skilled in the art would easily recognize that the Applicants had possession of the invention at the time the application was filed. Further, one skilled in the art would be able to identify homologous regions in the 5'-UTRs of other transcripts without undue experimentation.

Claim 19, which is also directed to a nucleic acid vector, also recites the downstream box and a nucleic fragment that enhances translation. For the reasons set forth above, the specification includes adequate description of both structure and function of the downstream box and nucleic acid fragment to clearly demonstrate possession of the invention to one skilled in the art. In addition, claim 19 recites a cold box and a second nucleic acid fragment derived from the first nucleic acid molecule or a second nucleic acid molecule, where that fragment represses expression of a cold shock inducible gene under physiological conditions. The structure and function of these elements are also adequately described in the specification to establish possession of the claimed invention.

For example, the specification describes at page 27, lines 1 through 12, a region within the 5'-UTR that has been identified as a new functional region. This region, located between

+56 and +117 of the 5'UTR of *cspA* includes sequences that mediate repression of *cspA* at 37°C. The sequence of the region is shown as a portion of Figure 14 and SEQ ID No:55. The structure and function of this region being set forth, it is evident that the applicants were in possession of the claimed invention.

The cold box as recited in claim 19 is also fully described in the specification, at, for example, page 25 line 16 through page 26 line 22. The specification identifies the function of the cold box as blocking the transient expression of a cold shock inducible gene so that expression can be continued for an extended period of time. In addition, this function is attributed to a region within the first 25 nucleotides of the 5'-UTR, and more specifically between +1 and +11 of the 5'-UTR. The specific sequence of the region is shown as a portion of Figure 14 and SEQ ID No:55 for the *cspA* transcript. Because the structure and correlated function of the cold box is fully set forth in the specification, the written description support for this element of claim 19 is also met.

Claims dependent upon claims 16 or 19 include the above-discussed elements, as well as other elements, such as coding regions, promoters or restriction sites, that are adequately described in the specification or well known to those skilled in the art. Thus, those claims dependent on claims 16 and 19 are also adequately described.

Claim 28 is also directed to a nucleic acid vector and recites elements similar to those discussed above for claims 16 and 19, including a first nucleic acid fragment that enhances translation of a cold shock inducible gene, a second nucleic acid fragment that represses expression of a cold shock inducible gene under physiological conditions, a cold box, a downstream box, a promoter and a restriction site. For the reasons discussed above, the specification includes adequate disclosure of the structures and functions of these elements to

demonstrate that the applicants had possession of the claimed invention. As such, claim 28 and its dependent claims 31 and 34, which further recite coding regions, have sufficient written description in the specification.

Claims 35-37 are directed to transformed bacteria containing certain of the claimed vectors. Methods of transforming bacteria with vectors are well known, and are also described, for example, beginning at page 29, line 22 of the specification and in the examples. Claims 35-37 are therefore adequately described by the specification.

Claims 38-49 are directed to methods of overexpressing a gene, involving the steps of transforming a bacteria with certain nucleic acid vectors and subjecting the bacteria to conditions that elicit a cold shock response. The vectors with which the bacteria are transformed include those having various combinations of elements, such as a downstream box, a cold box, a gene, a first nucleic acid fragment that enhances translation of a cold shock inducible gene, or a second nucleic acid fragment that represses expression of a cold shock inducible gene. As already noted, the step of transforming bacteria with a vector is generally known to those skilled in the art, and is also described in the specification. The step of subjecting the bacteria to conditions that elicit a cold shock response is described, for example, beginning at page 30, line 21 and in the examples that follow. Methods of subjecting bacteria to the other conditions recited in these claims are also well within the ordinary skill in the art. For the reasons set forth above, the various elements of the vectors used in the methods are well supported by the specification, and therefore satisfy the written description requirement.

Claims 50-56 are likewise supported by the written description of the specification. Independent claim 50 is directed to a vector having regulatory elements in a defined order; specifically: a promoter, at least a portion of a 5'-UTR of a cold shock inducible gene, a Shine-

Dalgarno sequence, a translation initiation codon, a downstream box, and at least one restriction enzyme recognition site for insertion of a heterologous gene. The structure and function of the promoter, Shine-Dalgarno sequence, translation initiation codon, downstream box, and restriction site as recited in claim 50 are well known to those skilled in the art, or have definite meaning and support in the specification for reasons already explained. The structure and function of the downstream box is discussed above in connection with claim 16.

The phrase "at least a portion of a 5'-UTR of a cold shock inducible gene" in claim 50 is similarly supported by the written description of the specification. The recited portion of the 5'-UTR of a cold shock inducible gene is a regulatory element. The specification includes several passages that describe regulatory elements in the 5'-UTR, many of which have already been discussed above. Examples include sequences that enhance translation of a gene under cold shock conditions, such as nucleotides from +123 to +135 of the 5'-UTR of the *cspA* transcript (SEQ ID No:48) (which is discussed in connection with claim 16 above) and sequences that mediate repression of *cspA*, such as nucleotides +56 and +117 of the 5'UTR of *cspA* (which is discussed in connection with claim 19). Thus, all of the elements of claim 50 are described in the specification in terms of both structure and corresponding function, and therefore satisfy the written description requirement. Dependent claims 51-56 add various elements similar to those already discussed. For the reasons already set forth, these claims are also supported by adequate written description in the specification.

Claim 57, which has been amended, recites an isolated nucleic acid molecule consisting essentially of between 8 and 25 nucleotides of the first 25 nucleotides of a 5'-UTR of a cold shock inducible mRNA transcript. This region contains the cold box. Support for amended claim 57 can be found in the specification, for example, on page 26, lines 3-10 and in the

examples. As discussed above, the structure and function of the claimed sequence, which includes the cold box, is adequately supported by the written description of the specification.

Because all of the elements recited in each of the pending claims are adequately described in the original specification by both structure and its corresponding function and this structure and corresponding function are recited in the pending claims, one skilled in the art would recognize that the Applicants possessed the claimed invention at the time the application was filed. Written Description Guidelines at 1106. Therefore, the written description requirement is met with respect to claims 1, 5, 6, 10, 14 and 16-57. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112 ¶ 1 is respectfully requested.

Claims Rejection Under 35 U.S.C. §102

Claims 1, 3, 5-15 and 57 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Goldstein et al. Claims 1, 3, 5-6 and 57 have also been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Oppenheim et al. (U.S. Patent No. 5,726,039). Claims 3, 7-9 and 11-13 have been cancelled. Claims 1, 5, 6, 10, 14, 15 and 57 have been amended to recite that their respective isolated nucleic acid molecules consist essentially of a given sequence or sequences.

Neither Goldstein nor Oppenheim disclose the particular sequences recited in claims 1, 5, 6, 10, 14, 15, and 57. These references describe the nucleic acids which contain the entire 5'-UTR, or which contain additional elements, such as Shine-Dalgarno sequences or promoters, that would materially change the nature of the claimed isolated nucleic acid molecules. Therefore, these references do not anticipate the rejected claims, and it is respectfully requested that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Goldstein and Oppenheim also do not specifically identify the particular nucleic acid sequences recited in claims 1, 5, 6, 10, 14, 15 and 57, and contain no teaching or suggestion that

it would be desirable to isolate these sequences. Claims 1, 5, 6, 10, 14, 15 and 57 are therefore also nonobvious over Goldstein and Oppenheim.

Double Patenting

Applicants acknowledge the rejection of claims 7-8 and 11-12 over claims 16-41 of U.S. Pat. No. 5,981,280 under the judicially created doctrine of obviousness-type double patenting. These claims have been cancelled, rendering the rejection moot.

Applicants acknowledge the obviousness-type double patenting rejection of claims 1, 3, 6-9 and 11-12 over claims 45-49 of U.S. Pat. No. 6,686,174. Of the rejected claims, claims 1 and 6 remain pending. As previously noted, claim 1 has been amended to recite that the nucleic acid molecule consists essentially of nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49, or SEQ. ID NO:50. By virtue of its dependency on claim 1, claim 6 also includes these elements. The sequences recited in claim 1 do not appear in claims 45-49 of U.S. Pat. No. 6,686,174, and there is no suggestion in U.S. Pat. No. 6,686,174 that the sequences recited in present claim 1 should be isolated. Thus, it is respectfully requested that the obviousness-type double patenting rejection of present claims 1 and 6 over claims 45-49 of U.S. Pat. No. 6,686,174 be reconsidered and withdrawn.

Miscellaneous Amendments

In addition to the amendments discussed above, claim 19 has been amended to make it more clear that the second nucleic acid fragment is derived from either the first nucleic acid molecule or from a second nucleic acid molecule. It has also been clarified that the vector is free from the first cold shock inducible gene. The scope of claim 19 has not been changed by these amendments.

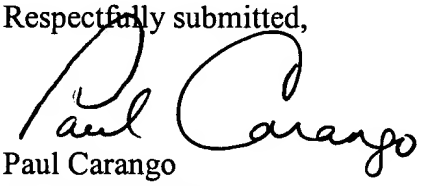
Claim 40 has been amended to remove reference to "said cold shock inducible gene", where a first and second cold shock inducible gene had been previously introduced in the claim. Specifically, it is now more clear in claim 40 that the second nucleic acid fragment can repress expression of the second cold shock inducible gene when the second nucleic acid molecule is derived from a second nucleic acid molecule that includes the second cold shock inducible gene. The scope of claim 40 has not been changed by this amendment.

The dependency of claim 47 has been changed from claim 43 to claim 46 in order to establish proper antecedence for "said temperature".

In addition to certain substantive amendments discussed above, claim 57 has been amended to correct obvious typographical errors.

In light of the foregoing, Applicants respectfully submit that the specification and claims as amended are now in condition for allowance, which is respectfully requested.

Respectfully submitted,



Paul Carango
Reg. No. 42,386
Attorney for Applicants

PC:SAN
215-656-3320